OPINION

The future developments in hepatology: no need for a jaundiced view

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Abstract

There have been major advances in the diagnosis and management of all forms of liver disease since the British Society of Gastroenterology first came into existence 75 years ago. In this review some of the exciting developments that are likely to enter into routine clinical practice over the next 5 years are highlighted. It is suggested that some critical changes need to take place in UK hepatology over the next decade to ensure that the management of liver disease in this country continues to be among the best in the world.

Introduction

When the British Society of Gastroenterology came into existence 75 years ago it would be safe to say that hepatology as a specialty would not have featured to any great extent. It was only in 1959 when Professor Dame Sheila Sherlock established the first liver unit in the world in a temporary wooden structure on the roof of the Royal Free Hospital that hepatology as a distinct entity came into existence. Since then there have been huge advances in our understanding of the aetiology, pathogenesis and management of acute and chronic liver diseases (CLDs). The introduction of orthotopic liver transplantation (OLT) into routine clinical care in the 1980s marked another significant milestone in the development of the specialty.¹ Yet despite this, liver disease mortality in the UK continues to increase, driven mainly by epidemics in obesity and alcohol consumption.² The number of deaths from liver disease in England alone rose from 9231 in 2001 to 11 575 in 2009 according to figures from the National End of Life Care Intelligence Network published in March this year, with 70% of these patients dying in hospital.³ This is also reflected in many different hospital admission statistics.

There was an 8.3% increase in hospital episodes for liver disease between 1998 and 2008 and this rate is likely to increase further. Indeed, in 2005 there were almost 44 000 hospital episodes with liver disease as the primary coded diagnosis and the death rate associated with each episode was 15.5%.⁴ This puts a large financial strain on the National Health Service given that each patient admitted with decompensated liver disease is estimated to cost £3400.⁴ Because most of these patients are younger than 60 and in their economically productive years this represents a significant economic and social burden on the whole of society.

Urgent public health measures are needed to tackle this epidemic of liver disease. There also needs to be increasing recognition that standards of care for patients with liver disease in the UK should be improved while ensuring that there is no inequity of access to hepatologists across the country. In this article we will initially deal with what we believe will be the most immediate advances in hepatology over the next 5 years and then go on to consider some of the significant changes that we suggest could and should happen over the next 10 years to improve the outlook for all patients with liver disease.

The 5-year outlook: where we should be

Viral hepatitis

The most significant changes in the next few years in the management of CLDs will be in the field of viral hepatitis. In 2011 the first two direct acting antiviral agents (DAAs) for the treatment of hepatitis C (HCV)—namely, telaprevir and boceprevir—were licensed.⁵ These two drugs are first-generation inhibitors of

the NS3/4A protease of HCV. They have both demonstrated excellent efficacy in the management of treatment-naïve patients with HCV genotype 1 as well as relapser-responders, improving treatment success in the former group from around 40% with standard care pegylated interferon (PEG-IFN) and ribavirin (RBN) to 67–73% with triple therapy.⁶ The National Institute of Health and Clinical Excellence (NICE) approved use of both drugs in March 2012 but it remains to be seen how widely available they will be given their considerable cost.

Many other DAAs are already in advanced phase 2 and phase 3 trials worldwide. These include second-generation protease inhibitors such as danoprevir and tegobuvir as well as polymerase and cyclophilin inhibitors.⁶ Most of these trials use the agents in combination with PEG-IFN and RBN, although the prospect of being able to use interferon-free regimens (with significantly fewer adverse drug reactions occurring as a result) is coming ever nearer. For example, a combination of the NS5A replication complex inhibitor daclatasvir and the NS3 protease inhibitor asunaprevir without PEG-IFN and RBN has been reported to lead to a sustained virological response (SVR; amounting to a cure) in 4 of 11 null responders with genotype 1 HCV treated in a phase 2a trial.⁷

Whereas telaprevir and boceprevir are only active against genotype 1, a lot of the newer agents have activity against the other HCV genotypes and it is hoped that treatment of genotype 4, in particular (which has traditionally been poorly responsive to current standard of care), will be revolutionised in the next few years.⁸ It appears that the HCV field is undergoing a rapid evolution with increasing complexity becoming inherent in treatment of this virus; similar to the experience in the HIV field a decade ago. This may result in specialist viral hepatologists having to supervise all clinical care of patients with complicated HCV whether directly or as part of regional multidisciplinary teams or networks.

The field of viral hepatitis has also ushered personalised medicine into hepatology. Genome-wide association studies have shown that interleukin-28b genotypes can significantly influence individual responses to PEG-IFN and RBN treatment, especially in genotype 1 HCV-infected patients.⁹ Patients with the favourable CC genotype have overall SVR rates of 76% compared with rates of 26% for those with the TT genotype. Heterozygote TC patients have intermediate SVR rates and this single genotype is thought to explain much of the difference in SVR rates between different ethnic groups.⁹ Many units have started to genotype their patients before deciding on whether to use the current standard of care or await the development of newer DAAs. The next few years should see such genotyping being widely adopted with newer markers of response to treatment also being identified.

There continues to be a UK-wide debate about universal vaccination for hepatitis B, although there are no plans for this to be adopted. The development of a vaccine for HCV is fraught with technical difficulties, primarily as traditional anti-envelope protein vaccines are unlikely to be efficacious given the viral diversity of HCV even within a given individual.¹⁰ Vaccination strategies have, therefore, been targeted at cellular immunity signalling but with no success.

Portal hypertension

All gastroenterologists and hepatologists deal with the consequences of portal hypertension in CLD every day. The mortality from variceal bleeding has been significantly reduced over the past few years with the widespread use of vasoactive agents, prophylactic antibiotics and improved basic resuscitation.¹¹ Despite these advances, mortality from variceal bleeding in the UK remains high at 15%.¹² Many of the deaths are in young men and women with alcoholic liver disease (ALD). A recent study in the *New England Journal of Medicine* reported that early intervention with transjugular intrahepatic portosystemic shunts (TIPSS) in selective patients with Childs Pugh B and C cirrhosis was associated with significant reductions in mortality.¹³ Implementing early TIPSS in the UK is, however, fraught with logistical problems. These include lack of intensive care beds as it is often unsafe to transfer these patients without intubation and access to level 3 beds. This problem is exacerbated by the patchy geographical provision of TIPSS services. There is also reluctance among many intensivists to admit such patients to level 3 beds owing to a perceived poor prognosis. Data are increasingly emerging that the latter perception is not borne out by fact and these obstacles can all be overcome if there is sufficient political will and the recognition that there is a need for a trained hepatologist in every hospital.¹⁴ In addition, prognostic markers, such as the Sequential Organ Failure Assessment score, increasingly allow prognosis to be assessed, and management (including decisions about ceilings of care) can be altered with continuous monitoring of the patient.¹⁵

Resistant ascites is another complication of portal hypertension that can be difficult to manage. Vasopressin V₂ receptor antagonists or 'vaptans' are an emerging class of drugs that may have a role in the treatment of resistant ascites and the hyponatraemia found in CLD.¹⁶ The largest analysis to date of the use of satavaptan in 1200 patients with cirrhosis failed to show a benefit. However, tolvaptan has recently been shown to be efficacious in a small trial of 18 patients and there are encouraging data from a trial of another vaptan M0002, although again this was with relatively small numbers of patients.¹⁶ The next few years will help to clarify the precise role for these agents. For selected patients with resistant ascites elective TIPSS can be beneficial, resulting in a

marked improvement in the patient's nutrition. For those patients in whom TIPSS is contraindicated, the implantation of a subcutaneous peritoneo-vesical shunt (the ALFA pump system) is an option that may well come into clinical practice over the next few years.¹⁶

Liver transplantation

OLT is arguably the best treatment for resistant ascites. Many other indications exist and the past decade has seen significant increases in the demand for OLT without any real increases in the supply of transplantable donor organs. This is reflected in the numbers on the waiting list; only 112 patients were waiting for OLT in 1999–2000 compared with 338 in 2008–9 and further increases are expected.¹ This is occurring in the context of an ever decreasing number of donations of a liver after brain death as a result of improvements in road safety, neurosurgical interventions and better management of hypertension in the community.¹⁷ Transplant centres have therefore had to resort to livers obtained from deceased after cardiac death (DCD) donors, although these organs can be associated with more postoperative complications such as acute kidney injury and biliary strictures.¹⁸ Optimising the condition of harvested DCD livers will be critical and this will be driven in the next few years by advances in surgical techniques and increasing use of extracorporeal perfusion methods that are currently in the experimental phase. Matching donor to recipient is an area which is rightly receiving more attention in order to maximise utility of liver grafts.¹⁹

Increasingly recipients with medical comorbidities are being considered for OLT and this is especially true for patients with non-alcoholic fatty liver disease (NAFLD), an ever increasing indication for OLT in the Western world.²⁰ Management of patients after OLT is, as a result, becoming more complex. Traditional immunosuppressive agents—especially the calcineurin inhibitors tacrolimus and ciclosporin—are associated with significant risk of chronic renal impairment, diabetes, hypertension and malignancy and this has driven the development of newer agents.²¹ These have mainly been designed to target costimulatory signals to T cells. Agents such as alfarecept, which targets lymphocyte trafficking through inhibition of leucocyte function associated antigen-3, and belatacept, which inhibits costimulation by cytotoxic lymphocyte antigen-4, have shown some promise in early phase 3 trials in patients with a renal transplant and have been used as part of CNI calcineurin inhibitor-free regimens.^{22–23} Trials in patients with a liver transplant are continuing. Patients with transplants owing to HCV present a particular challenge of immunosuppression as they are all universally reinfected with the virus. Ciclosporin use has been reported to be associated with less significant fibrosis than tacrolimus in some studies.²¹ However, this finding is not consistent and more research into

this area is critical in order to improve the prognosis of patients receiving a transplant for HCV.

One of the most challenging problems the transplant community will have to deal with in the next few years is the increasing availability of generic immunosuppressants such as tacrolimus. While bio-availability equivalence can be demonstrated for these agents in the non-transplant population, there are some reports of serious adverse events occurring when patients are switched, although a recent trial (with limited follow-up), suggested that patients can be safely switched.^{24–25}

Alcoholic liver disease

All the developments so far discussed are occurring against a background of what can best be described as an 'epidemic' of ALD, which is affecting the UK disproportionately to mainland Europe.²⁶ Standardised age-adjusted mortality from ALD has now increased fivefold from the mid-1970s at the same time as mortality from cancer and cardiovascular disease has fallen. Liver cirrhosis is now the fifth most common cause of death in the UK. This is a serious problem as many young people are dying from ALD in the economically productive part of their lives.²⁷ Much can be done on the public health front and we believe that recent political initiatives throughout the UK to introduce minimal alcohol pricing (for which the Royal College of Physicians and the British Society of Gastroenterology have long campaigned) should start to have an effect in the next 5 years if adopted by the various UK legislative bodies. It is also evident that these patients present to medical services for other reasons long before they are formally diagnosed with ALD. This is a golden opportunity for all medical professionals to provide advice on alcohol harm reduction. Mounting evidence shows that these so-called 'brief interventions' substantially reduce alcohol consumption in selected individuals.²⁸

Patients often present for the first time with acute alcoholic hepatitis (AAH)—a condition that still carries a significant 30-day mortality.²⁹ The debate about whether or not corticosteroids are effective continues in many circles and the National Institute of Health Research (NIHR)-sponsored STOPAH trial (Steroids or Pentoxifylline for Alcoholic Hepatitis) of 1200 patients that is actively recruiting throughout the UK should give us a definitive answer in the next 2–3 years. The role of N-acetylcysteine (NAC) is also the subject of much debate, with a recently published study in the *New England Journal of Medicine* demonstrating a survival benefit at 1 month for patients given corticosteroids with NAC compared with those given corticosteroids alone.³⁰ However, this benefit did not extend to 6-month survival and the routine use of NAC cannot be recommended. A more recent and controversial development came with the publication of a trial of OLT in selected patients with AAH not responsive to corticosteroids (using the Lille criteria)

from a multicentre trial conducted in France and Belgium.³¹ In that paper the authors showed that in the 26 patients selected for early OLT the 6-month survival was 77% compared with 23% in patients not offered OLT. Expanding UK OLT criteria to include selected patients with a first presentation of AAH is controversial. However, in the light of the above results can we ethically deny the option of OLT in a small but highly selected few?

Non-alcoholic fatty liver disease

As alluded to above, NAFLD is a condition whose prevalence is continuing to rise in the Western world with increasing rates of obesity.³² This is particularly worrying as rates of childhood obesity are also rising; something which has gained political recognition. Postmortem data from the USA suggest that teenagers are developing cirrhosis as a result of NAFLD and there is no reason to suspect that the UK lags too far behind this trend.³² The next few years are likely to see younger and younger people diagnosed with NAFLD cirrhosis. Hepatocellular cancer (HCC) is also strongly linked to obesity; more so than any other cancer in men and rates of this are also likely to rise in the Western world.³³ Work is already under way to develop treatments to prevent progression of steatohepatitis to full-blown cirrhosis in NAFLD. The NIHR sponsored FELINE trial investigating the use of the angiotensin 2 receptor blocker losartan as an antifibrotic is currently recruiting in the UK and should report its findings in the coming 2–3 years.

Hepatocellular cancer

HCC rates are increasing throughout the world driven by many of the factors already discussed. Locoregional treatments such as transarterial chemoembolisation and radiofrequency ablation have significantly improved the prognosis for many patients with HCC. The use of these interventions to downgrade patients to within transplant criteria is an active area of research.³⁴ The multiple tyrosine kinase inhibitor sorafenib has now entered routine clinical practice for the management of patients with HCC not suitable for other interventions. Its use in combination with transarterial chemoembolisation is the subject of trials that should report in the next few years. Second-generation tyrosine kinase inhibitors with theoretically fewer side effects are also being developed.³⁴

Liver fibrosis and its reversal

There have been great advances in our understanding of the molecular and cellular basis of liver fibrosis in the past two decades or so. This has changed the dogma that liver cirrhosis is irreversible. A large number of agents have shown great promise in the experimental field in halting or even reversing the progression of fibrosis.³⁵ Indeed, experimental studies suggesting that warfarin has a significant antifibrotic effect has resulted in the WAFT-C trial investigating

the antifibrotic effects of warfarin in patients who have had an OLT for HCV.³⁶ There remain, however, real barriers to translating these discoveries into the clinical field, which is discouraging major pharmaceutical involvement in antifibrotic drug development. Chief among these is the reliance on liver biopsies with their inherent problems of sampling error and complications.³⁵ Non-invasive monitoring of fibrosis using Fibroscan and serum markers now forms part of routine clinical practice, although their sensitivity for intermediate stages of fibrosis is questionable and there are insufficient data on the value of serial measurements using these markers. MRI elastography is a technique that is showing much promise and it is hoped that in the next few years more data will emerge about its usefulness in routine clinical practice.³⁷ Cost will be one of the main limitations. Finally, there is a desperate need for the development of a non-invasive marker of actual liver function—the hepatological equivalent of the estimated glomerular filtration rate—to enable liver clinicians to monitor their patients with known cirrhosis. However, perhaps the greatest need is to aid primary care doctors in identifying which patients require referral to secondary care. We hope that the next few years will see some progress in this area.

The 10-year outlook: how hepatology needs to change

There are clearly many exciting developments in the pipeline. Despite this, many fundamental challenges face the UK and international hepatology over the coming decade.

Palliative care in hepatology

One of the areas that needs addressing is the role of palliative care in hepatology, especially in patients with end-stage liver disease where cirrhotic cachexia and recurrent ascites substantially lower quality of life.³⁸ Data from the National Survey of Patient Activity in palliative care suggest that liver disease is under-represented in referrals to palliative care and this is something that needs addressing urgently.³⁹ High-level political discussions about who provides the service and how it should be resourced are needed. The status quo cannot continue.

Molecular hepatology

The era of molecular hepatology is well and truly upon us as shown by the importance of interleukin-28 genotyping in HCV.⁴⁰ The UK has traditionally been slow to adopt new technologies and treatments and this has not been helped by the long waiting lists at NICE to evaluate these. We are likely to see new advances in stratifying the risk of alcoholic patients developing ALD based on their genomes; a current US National Institute of Health study, in which the UK is participating, is examining this. Molecular signatures of specific HCC will influence the modality of treatment that individual patients receive.⁴¹ The recently instigated

PIANO trial of an anti-CXCL10 monoclonal antibody in patients with primary biliary cirrhosis for whom conventional treatment has failed is an example of the increasing use of small-molecule treatment in hepatology.⁴² Advances in liver stem cell research may start to have an impact on patient care over the next decade. If we wish our patients to benefit from these advances, we must actively lobby for the increasing recognition of liver disease as a priority area in both the research and the treatment fields.²

Liver support systems and advances in transplantation

We will continue to see young patients die of both acute and acute-on-chronic liver failure, largely associated with alcohol abuse. The traditional thinking that these patients have a poor prognosis has hampered their access to intensive care facilities.¹⁴ This is wrong and we must communicate this to our intensive care colleagues. This is where the transplant centres and tertiary referral liver centres can aid in the education of the regional units. The development of artificial and bio-artificial liver support technologies would greatly advance this case.⁴³ Although these systems have been under development for over 30 years, advances in the understanding of the pathophysiology of hepatic encephalopathy coupled with better biocompatibility of these devices may mean that significant progress will occur over the next few years.

There are other controversial concerns that require discussion and debate over the next decade. Given the scarcity of donor organs and the increasing number of patients on the waiting list we need to seriously consider alternative strategies for bridging patients with acute and acute-on-chronic liver failure. An opt-out system of organ transplantation has been adopted by Spain, resulting in one of the best organ procurement rates in the world.¹⁷ While we appreciate that there are complex ethical and legal issues associated with this, we believe that the UK should seriously investigate the possibility of changing legislation to introduce such a system.⁴⁴ This is something that the Welsh government has recently hinted that it might adopt. The uptake of live related OLT in the UK is poor compared with countries like India and South Korea.¹ We believe that we need to change attitude as well as our expertise over the coming decade. This will allow us to have more informed discussions with our patients and the general public.

Workforce planning

Finally, there are serious issues about how hepatology services should be delivered in the UK and who should deliver them. How do we reconcile the fact that only 15% of the gastrointestinal (GI) workforce are hepatologists and that two-thirds of these are in liver transplant or tertiary referral centres with the fact that 60% of inpatient GI care and up to 30% of new outpatient work at least in England is liver related (Professor Martin Lombard, personal communication)?

The provision of specialist hepatology centres is geographically patchy across the UK and patients often have to travel long distances to access them. UK hepatology training has changed over recent years but more needs to be done to ensure that trainees specifically wanting to train in hepatology are allowed the flexibility to do so and, more importantly, that there are consultant jobs for which they can apply.

The National Liver Plan specifies that by 2016 all district general hospitals should have an accredited hepatologist in post, which would greatly improve access to specialist input and raise standards of care.⁴⁵ Unfortunately, the current economic environment is likely to mean that we will fall well short of this target. One approach is to aim to increase the standard of care across all GI units in the country. The Global Rating Score has revolutionised care and standards in endoscopy; a similar approach in hepatology might be the catalyst that is required to drive standards forward and bring recognition of the problem to the fore. But we need chief executives in trusts to recognise the benefit of trained hepatologists.

We believe that another approach should be to train a new type of hepatologist—a so-called ‘community hepatologist’. These individuals would be able to deliver care closer to the patient homes and may take a lead role in the development of palliative care for individuals with end-stage liver disease (see above). They could be funded by primary care with secondary care support. General practitioner consortia could employ these individuals and we should be lobbying for this in the next 1–2 years as the consortia come into existence. Shared-care protocols should, in our opinion, enable more patients with early liver disease to be managed in the community both by general practitioners and by hepatologists in outreach settings. These are all developments that are already underway in some parts of the country—for example, hepatitis outreach services run by both our units.

The increasing complexity of the management of viral hepatitis raises the question of whether or not there is a ‘critical mass’ of patients that each individual clinician needs to be managing in order to have access to some of the newer DAAs (see above). We envisage the evolution of regional viral hepatitis multidisciplinary networks, allowing continuous communication between clinicians in the ‘periphery’ and ‘centres’. Such joint management will ultimately benefit our patients.

Conclusions

We have come a long way in UK hepatology since the British Society of Gastroenterology was first established 75 years ago. The next 10 years will arguably see an even more rapid pace of development of therapeutics for all forms of liver disease. It is critical for the whole GI community to be at the forefront of these changes always remembering that our prime responsibility

should be ensuring that our patients have access to the best care possible.

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